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Association between periodontitis and bipolar disorder

A nationwide cohort study

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Abstract

Whether periodontitis is a risk factor for developing bipolar disorders (BD) has not been investigated. We aimed to determine whether periodontitis is associated with the subsequent development of BD and examine the risk factors for BD among patients with periodontitis.

Using ambulatory and inpatient claims data from the National Health Insurance Research Database (NHIRD), we identified 12,337 patients who were aged at least 20 years and newly diagnosed with periodontitis between 2000 and 2004. The date of the first claim with a periodontitis diagnosis was set as the index date. For each patient with periodontitis, 4 subjects without a history of periodontitis were randomly selected from the NHIRD and frequency-matched with the patients with periodontitis according to sex, age (in 5-year bands), and index year.

The periodontitis group had a mean age of 44.0 ± 13.7 years and slight predominance of men (51.3%). Compared with the subjects without periodontitis, the patients with periodontitis had higher prevalence of diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, head injury, major depressive disorder, chronic obstructive pulmonary disease (COPD), and asthma ($P < .001$). The incidence rate of BD was higher in the periodontitis group than in the non-periodontitis group (2.74 vs 1.46 per 1000 person-year), with an adjusted hazard ratio of 1.82 (95% confidence interval = 1.59–2.08) after adjustment for sex, age, and comorbidities.

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K-H C and Y-C H have contributed equally to this work.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. The dataset is owned by the Taiwan National Health Research Institutes (NHRI). Requests for the data set may be sent an e-mail to the NHRI at nhird@nhri.org.tw or call at +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).

The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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The patients with periodontitis exhibited a significantly higher risk of developing BD. Keep the better oral hygiene to reduce periodontitis might be a preventive strategy for BD.

Abbreviations: BD = bipolar disorders, CIs = confidence intervals, DM = diabetes mellitus, HPA = hypothalamic–pituitary–adrenal, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IHD = ischemic heart disease, ILs = interleukins, LHID2000 = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PGE2 = prostaglandin E2, PVN = paraventricular nucleus, SDs = standard deviations, TNF-α = tumor necrosis factor alpha.

Keywords: bipolar disorder, hazard ratio, National Health Insurance Research Database, periodontitis

1. Introduction

Periodontitis is initiated by bacterial plaque biofilm[1] and can be caused by gingivitis affecting soft tissues near the teeth, resulting in the destruction of the tissue supporting the teeth.[2] Periodontal tissues respond to bacterial invasion by mobilizing defense cells and releasing inflammatory cytokines, such as interleukins (ILs),[3–5] tumor necrosis factor alpha (TNF-α),[6,7] and prostaglandin E2 (PGE2),[7] which may cause tissue destruction by stimulating the production of enzymes such as matrix metalloproteinase.[8] Evidence is mounting for possible associations between periodontitis and other diseases such as,[9,10] depression,[11] diabetes mellitus (DM),[12] atherosclerotic cardiovascular disease,[13–15] and rheumatoid arthritis.[16–18]

Bipolar disorder (BD) is a disabling, recurrent mental illness that varies widely in severity. The onset of BD is typically observed in late childhood or early adolescence.[19] Patients with BD have higher rates of comorbidities of psychiatric disorders and other medical conditions, which might entail an increased medical burden and multiple physical abnormalities.[20] Early detection and treatment of BD can improve patient outcomes.[19] One study suggested that patients with BD are at high risk of dental diseases.[21] When patients are in depressive episodes, they pay less attention to oral hygiene, leading to an increase in dental caries, and periodontal disease.[22] By contrast, when patients are in a manic period, they may overuse oral health aids, which has been correlated with the increased incidence and severity of cervical injuries and occasional mucosal or gingival wounds.[23] Furthermore, drug treatments, such as antidepressants and antipsychotics, have been demonstrated to cause moderate-to-severe xerostomia, which can exacerbate dental diseases.[24]

Although the association between periodontitis and psychiatric conditions, such as major depressive disorders and cognitive decline, remains controversial,[25,26] periodontitis has been suggested as a risk factor for dementia.[9,10] Whether periodontitis is a risk factor for developing subsequent BD has not been investigated. In this study, we hypothesized that periodontitis increases the risk of BD. To test our hypothesis, we conducted a nationwide population-based study to investigate the incidence and risks of BD among patients with or without periodontitis.

2. Patients and methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was implemented in 1995. At the end of 2014, the program was providing health care to approximately 99% of the Taiwan population (23.75 million people). The NHI is a mandatory health insurance program that offers comprehensive medical care coverage to all residents of Taiwan. The National Health Insurance Research Database (NHIRD) is managed and maintained by the National Health Research Institutes (NHRI) according to the directives of the National Health Insurance Administration. Our study used the Longitudinal Health Insurance Database (LHID2000), which contains the data of 1 million enrollees sampled from the medical claim records of the NHI from 1996 to 2011. The LHID2000 contains comprehensive outpatient and inpatient data, including demographic, clinical visit, and prescription information, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To ensure privacy protection, the NHRI encrypts and converts the identification numbers of all NHIRD records before releasing them for research. Our study was exempted from review by the Institutional Research Ethics Committee of China Medical University (CMU-REC-101-012), Taiwan.

2.2. Study population

Using the ambulatory and inpatient claims data sets, the inclusion criteria for this study of patients with periodontitis included being 20 years old or older and newly diagnosed with periodontitis (ICD-9-CM 523.4x and 523.5x) between 2000 and 2004. The date of the first claim with a periodontitis diagnosis was considered as the index date. For each patient with periodontitis, 4 subjects with no history of periodontitis (ICD-9-CM 523.xx) were randomly selected from the NHIRD and frequency-matched according to sex, age (in 5-year bands), and index year. The definition of BD patients was based on the following criteria: patients with a diagnosis of BD (ICD-9-CM code 296.xx) at least 3 times before the index date. However, patients who developed BD within 1 month after the index date were excluded. Finally, the periodontitis and non-periodontitis groups comprised of 12,337 and 49,348 patients, respectively. The ICD-9 code 523.4 includes the symptoms of chronic periodontitis, including chronic pericoronitis, chronic pericementitis, periodontitis (no otherwise specific, complex, and simplex), but excludes chronic apical periodontitis (ICD 9 code: 522.6). ICD-9 code 523.5 refers to the type of periodontitis with diffuse atrophy of the alveolar bone.

Demographic data included sex and age (20–34 years, 35–49 years, 50–64 years, and ≥65 years). We also recorded claims data on comorbidities before the index date on DM (ICD-9-CM 250.xx), hyperlipidemia (ICD-9-CM 272.xx), hypertension (ICD-9-CM 401.xx-405.xx), ischemic heart disease (IHD, ICD-9-CM 410.xx-414.xx), stroke (ICD-9-CM 430.xx-438.xx), head injury (ICD-9-CM 850.xx-854.xx and 959.01), alcohol abuse and dependence (ICD-9-CM 303.xx, 305.0x, and V11.3), major depressive disorder (ICD-9-CM 296.2x, 296.3x, 311. xx,

Table 1

Baseline demographic factors and comorbidities of patients according to periodontitis status.

Characteristics		Non-periodontitis N = 49,348		Periodontitis N = 12,337		*P* value
		n	%	n	%	
Men		25328	51.3	6332	51.3	.99
Age, y	20–29	8984	18.2	2246	18.2	.99
	30–39	10508	21.3	2627	21.3	
	30–49	14256	28.9	3564	28.9	
	≥50	15600	31.6	3900	31.6	
Mean (SD)*		43.9	(13.9)	44.0	(13.7)	.67
DM		2652	5.37	787	6.38	<.001
Hyperlipidemia		3430	6.95	1615	13.1	<.001
Hypertension		7476	15.2	2196	17.8	<.001
IHD		2796	5.67	1006	8.15	<.001
Stroke		878	1.78	113	0.92	<.001
Head injury		702	1.42	123	1.00	<.001
Alcohol abuse/dependence		61	0.12	9	0.07	.18
Major depressive disorder		378	0.77	206	1.67	<.001
COPD		1822	3.69	637	5.16	<.001
Asthma		1165	2.36	385	3.12	<.001
Tobacco dependence		19	0.04	0	0.00	–

COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, IHD = ischemic heart disease, SD = standard deviation.
* Student *t* test.

300.4x, and 309.0x). Smoking status and alcohol consumption were not available in NHIRD. Thus, we performed the multivariate analysis by adjusting for tobacco related diseases (including tobacco dependence [ICD-9-CM codes 305.1], chronic obstructive pulmonary disease [ICD-9-CM codes 490–492, 494, and 496], and asthma [ICD-9-CM code 493]).

The primary outcome was a diagnosis of BD (ICD-9-CM code 296.xx), which was determined by linking the NHIRD ambulatory and inpatient data. All study participants were observed from the index date to BD diagnosis, withdrawal from the NHI program, or the end of 2011.

2.3. Statistical analysis

Summary statistics are expressed as frequencies and percentages for categorical data and means and standard deviations (SDs) for continuous variables. The Pearson chi-square test and Student *t* test were used to compare categorical and continuous variables, respectively, between the patients with and without periodontitis. The sex-, age-, and comorbidity-specific incidence rates of BD were measured for both groups. The Kaplan–Meier method was used to depict the cumulative incidence of BD for the groups. The log-rank test was used to test the difference between the curves. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for determining whether periodontitis is a risk factor for the development of BD, and the models were adjusted for sex, age, DM, hyperlipidemia, hypertension, IHD, stroke, head injury, alcohol abuse/dependence, and major depressive disorder. We also performed sex-, age-, and comorbidity-stratified analysis to investigate the association between periodontitis and the risk of BD. All the data processing and statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). A 2-sided *P* value of <.05 was considered statistically significant.

3. Results

We identified 12,337 patients with periodontitis from 2000 to 2004 as the periodontitis group and frequency-matched them with 49,348 subjects without periodontitis according to sex, age, and year of periodontitis diagnosis. Table 1 contains the demographics and comorbidities of the patients with and without periodontitis. The mean age of the periodontitis group was 44.0 years (SD = 13.7 years), with a slight predominance of men (51.3%). The patients with periodontitis had higher prevalence of DM, hyperlipidemia, hypertension, IHD, stroke, head injury, and major depressive disorder, chronic obstructive pulmonary disease (COPD), and asthma than the subjects without periodontitis (all $P < .001$).

Figure 1 showed the results of the log-rank test and the cumulative incidences of BD. The Kaplan–Meier analysis was used to determine the risk of BD during follow-up in both groups. The cumulative incidence of BD was significantly higher in the periodontitis group than in the non-periodontitis group ($P < .001$).

During the average follow-up of 8.79 years, 339 (2.76%) patients in the periodontitis group and 611 (1.46%) patients in the non-periodontitis group developed BD. The incidence rate of BD was higher in the periodontitis group than in the non-periodontitis group (2.76 vs 1.46 per 1000 person-year), with an adjusted HR (aHR) of 1.82 (95% CI = 1.59–2.08) after adjustment for sex, age, and comorbidities (Table 2). In a multivariate Cox regression analysis, men exhibited a lower risk of BD than women did (aHR = 0.59, 95% CI = 0.52–0.68). Compared with the patients without counterpart comorbidities, higher risks of BD were observed in those with comorbidities of hyperlipidemia (aHR = 1.42, 95% CI = 1.16–1.74), hypertension (aHR = 1.34, 95% CI = 1.11–1.62), IHD (aHR = 1.52, 95% CI = 1.22–1.89), head injury (aHR = 1.85, 95% CI = 1.23–2.79), alcohol abuse or dependence (aHR = 9.43, 95% CI = 4.66–19.1), major depressive disorder (aHR = 7.42, 95% CI = 5.86–9.41), and COPD (aHR = 1.36, 95% CI = 1.04–1.77).

Stratified by sex, the higher risks of BD in patients with periodontitis were exhibited by both women (aHR = 1.68, 95% CI = 1.42–2.00) and men (aHR = 1.87, 95% CI = 1.51–2.32) compared with the subjects without periodontitis. Stratified by age group, the patients with periodontitis had a significantly

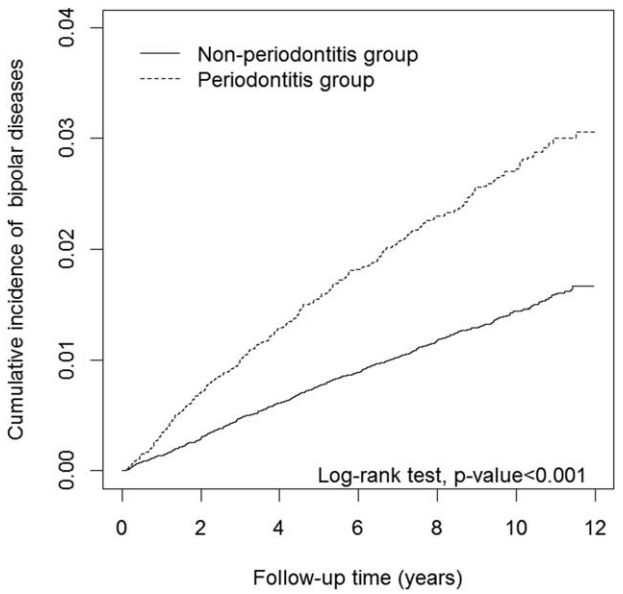

Figure 1. Comparison of the cumulative incidence of bipolar in the periodontitis cohort and non-periodontitis group.

higher risk of BD compared with the subjects without periodontitis in all age categories. The aHRs of BD were 1.76 (95% CI = 1.26–2.45) for those aged 20 to 29 years, 1.80 (95% CI = 1.32–2.47) for those aged 30 to 39 years, 1.74 (95% CI = 1.33–2.27) for those aged 40 to 49 years, and 1.68 (95% CI = 1.35–2.08) for those aged 50 years or older. Regardless of the subjects' comorbidity status, patients with periodontitis had a higher risk of BD than subjects without periodontitis (aHR = 1.80, 95% CI = 1.50–2.16 for those without comorbidity and aHR = 1.78, 95% CI = 1.47–2.17 for those with comorbidity) (Table 3).

4. Discussion

Periodontitis is a highly prevalent oral disease initiated by a bacterial plaque biofilm[1] around the teeth resulting in chronic inflammation in adjacent soft tissue. In routine dental procedures, even tooth brushing, these bacteria and their components, such as endotoxin, can be easily disseminated into the systemic circulation through minor or major gingival injuries. Notably, in immunocompromised people or patients with preexisting pathologic oral conditions, bacteremia may lead to the bacterial infection of distant organs, which may elicit immunological

Table 2

Cox model measured hazards ratios and 95% confidence intervals of bipolar disorder associated with periodontitis and covariates.

Characteristics	BP no.	PY	IR	HR (95% CI)	
				Crude	Adjusted*
Periodontitis					
No	611	419861	1.46	1.00	1.00
Yes	339	122641	2.76	1.91 (1.68–2.18)	1.82 (1.59–2.08)
Sex					
Women	588	267440	2.20	1.00	1.00
Men	362	275062	1.32	0.60 (0.52–0.68)	0.59 (0.52–0.68)
Age, y					
20–29	152	92705	1.64	1.00	1.00
30–39	173	115906	1.49	0.91 (0.73, 1.13)	0.91 (0.73–1.13)
40–49	249	164788	1.51	0.92 (0.75, 1.13)	0.86 (0.70–1.05)
≥50	376	169103	2.22	1.35 (1.12, 1.63)	0.94 (0.76–1.16)
DM					
No	865	515277	1.68	1.00	1.00
Yes	85	27225	3.12	1.85 (1.48–2.31)	1.07 (0.84–1.37)
HL					
No	791	497659	1.59	1.00	1.00
Yes	159	44843	3.55	2.23 (1.88–2.64)	1.42 (1.16–1.74)
HT					
No	700	460264	1.52	1.00	1.00
Yes	250	82238	3.04	1.99 (1.72–2.30)	1.34 (1.11–1.62)
IHD					
No	820	510702	1.61	1.00	1.00
Yes	130	31800	4.09	2.54 (2.11–3.05)	1.52 (1.22–1.89)
Stroke					
No	926	535937	1.73	1.00	1.00
Yes	24	6565	3.66	2.09 (1.39–3.13)	1.30 (0.85–1.97)
Head injury					
No	926	535585	1.73	1.00	1.00
Yes	24	6917	3.47	2.00 (1.33–2.99)	1.85 (1.23–2.79)
Alcohol abuse					
No	942	541941	1.74	1.00	1.00
Yes	8	561	14.3	8.15 (4.06–16.34)	9.43 (4.66–19.1)
MDD					
No	867	538028	1.61	1.00	1.00
Yes	83	4474	18.6	11.4 (9.13–14.3)	7.42 (5.86–9.41)
COPD					
No	875	523131	1.67	1.00	1.00
Yes	75	19371	3.87	2.30 (1.82, 2.01)	1.36 (1.04–1.77)
Asthma					
No	905	529718	1.71	1.00	1.00
Yes	45	12784	3.52	2.05 (1.52, 2.77)	1.19 (0.86–1.65)

BP no. = number of patients with BP, CI = confidence interval, DM = diabetes mellitus, HL = hyperlipidemia, HR = hazard ratio, HT = hypertension, IHD = ischemic heart disease, IR = incidence rate, MDD = major depressive disorder, per 1000 = person-years, PY = person-years.

* Adjusted for periodontitis, sex, age (categorical), and comorbidity in Cox proportional hazards regression.

Table 3

Incidence rates and hazard ratios of bipolar disorder according to periodontitis status and stratified by sex, age, and comorbidities.

	Periodontitis						Compared to non-periodontitis group	
	No			Yes			HR (95% CI)	
Characteristics	BP no.	PY	IR	BP no.	PY	IR	Crude	Adjusted†
Sex								
Women	385	207586	1.85	203	59853	3.39	1.84 (1.55–2.18)	1.68 (1.42–2.00)
Men	226	212275	1.06	136	62788	2.17	2.06 (1.66–2.55)	1.87 (1.51–2.32)
Age, y								
20–29	96	70086	1.37	56	22620	2.48	1.84 (1.33, 2.56)	1.76 (1.26–2.45)
30–39	110	89439	1.23	63	26467	2.38	1.93 (1.41, 2.63)	1.80 (1.32–2.47)
40–49	164	129226	1.27	85	35562	2.39	1.89 (1.45, 2.46)	1.74 (1.33–2.27)
≥50	241	131111	1.84	135	37993	3.55	1.96 (1.58, 2.42)	1.68 (1.35–2.08)
Comorbidity status*								
No	362	325020	1.11	173	85537	2.02	1.81 (1.51, 2.17)	1.80 (1.50–2.16)
Yes	249	94841	2.63	166	37104	4.47	1.74 (1.43, 2.12)	1.78 (1.47–2.17)

BP no. = number of patients with BP, CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 = person-years, PY = person-years.

* Patients with a comorbidity of diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, head injury, alcohol abuse or dependence, major depressive disorder, COPD, asthma, and tobacco dependence were enrolled in the comorbidity group.

† Mutually adjusted for sex, age (continuous), and comorbidity in Cox proportional hazards regression.

responses. Oral bacteria and endotoxins have also been associated with the occurrence of lung infection, sepsis, liver disease, and infective endocarditis,[1] but not with BD.

Our results revealed that the patients with periodontitis were at a significantly increased risk of BD. According to our analysis of the risk factors for BD in patients with periodontitis, we suggested that a possible mechanism is the interaction between chronic inflammation and the hypothalamic–pituitary–adrenal (HPA) axis. The key structures comprising the HPA axis are the paraventricular nucleus (PVN) of the hypothalamus, anterior lobe of the pituitary gland, and adrenal gland.[27,28] In addition, recent studies have demonstrated that chronic inflammation is associated with BD.[29–32] The immune reaction and proinflammatory cytokines, such as ILs and TNF-α, could induce neuroinflammation.[33] Lipopolysaccharide, a membrane component of Gram-negative bacteria, is an endotoxin and has been shown to stimulate microglia to produce numerous proinflammatory cytokines in the brain, such as TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6).[34] Likewise, inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-17 have been shown to be increased in patients with chronic periodontitis. Elevated secretion of these cytokines contributes to acute and chronic inflammation and tissue injury, leading to increased risk of systemic diseases such as cardiovascular diseases, DM, cancer, and chronic respiratory diseases.[35–37] Interestingly, the serum levels of anti-inflammatory cytokines, IL-4, and IL-10 were reduced in patients with chronic periodontitis.[37,38] Therefore, periodontitis may result in a local infection and thereafter induce inflammatory cascades, thus increasing the susceptibility to other severe pathological conditions such as cardiovascular disease[39,40] and DM.[41] Notably, it has been shown that proinflammatory cytokines, such as IL-1β, can be detected in PVN. The upregulation of IL-6 and COX-2 has also been detected in the adrenal glands. These findings provide novel insight into the relationship between proinflammatory cytokines within key structures comprising the HPA axis.[27] Furthermore, chronic inflammation may disturb the HPA axis and induce hypercortisolemia and neuroinflammation through a proinflammatory cascade.[27,42,43] In addition to inducing neuroinflammation, proinflammatory cytokines could also induce indoleamine 2,3-dioxygenase, thus reducing the availability of tryptophan and disturbing serotonin synthesis.[44] Immune-inflammatory pathways and cytokine changes in BD have been linked to changes in oxidative stress, nitrosative stress, and tryptophan catabolites.[44] As a result, the risk of BD was increased among patients with periodontitis.

It has been reported that periodontitis is a risk factor of dementia. That is not a concrete causality research, instead that is an association study. Two research designs have been used on the similar topics, namely case-control study[10] and retrospective cohort study.[45] For the case-control study, they enrolled the cases with (experimental group) or without (control group) cognitive impairment or dementia, and analyzed the association with periodontitis to evaluate its risk to dementia.[10] For the retrospective cohort study, they enrolled the patients diagnosed with periodontitis during 2003 to 2004, followed up for overall dementia, Alzheimer disease, and vascular dementia until 2015, and retrospectively analyzed the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of dementia according to chronic periodontitis.[45] The experimental design of our current study was similar to the later one as a retrospective cohort study. Periodontitis represented a source of systemic inflammation,[46] and chronic inflammation is associated with dementia,[9,10,47] as well as BD,[29–32] suggesting that the mechanism of periodontitis increasing the risk to dementia and BD might share similar factors, at least in part, including inflammation.

In addition to inflammation, smoking is also a common risk factor for both periodontitis and BD. A previous study demonstrated that smoking and oral pain are factors related to the prevalence and risk of periodontitis among adults with or without DM.[48] Similarly, smoking is about 2 to 3 times common in adults with BD compared with the general population.[49] The associations may be related to lower levels of serotonin, which contributes to brain serotonergic function[50,51] in smokers. The associations between smoke-related diseases such as COPD, asthma, and tobacco dependence with periodontitis and BD were also evaluated in the current study. The results showed that the patients with periodontitis had higher prevalence of COPD and asthma compared with those without periodontitis (Table 1), and the patients with BD had higher risk of COPD (aHR 1.36, 95%

CI 1.04–1.77) (Table 2). However, we could not examine the effect of tobacco dependence due to the limited patients being tobacco dependent (only 19 in the non-periodontitis group and no patient in the periodontitis group).

This population-based study specifically examined periodontitis as a risk factor for BD by using matched cohorts. The major finding of our study is the higher incidence of subsequent BD among patients with periodontitis. Furthermore, the patients with periodontitis exhibited higher prevalence of DM, hyperlipidemia, hypertension, IHD, stroke, head injury, and major depressive disorder than the patients without periodontitis (all $P < .001$) (Table 1). Notably, the male patients exhibited a lower risk of BD than the female patients did (aHR = 0.60, 95% CI = 0.52–0.68). Women have been demonstrated as having a higher rate of thyroid hormone disturbances as well as thyroid diseases and autoimmunity, which hinder BD treatments using lithium.[52] Thyroid hormones have been shown to regulate the functions and regeneration of the adult central nervous system.[53] Thyroid hormones were also suggested as worsening periodontal diseases, and disturbance of thyroid hormones may lead to the destruction of the periodontium.[54]

On the other hand, the mean age of the patients with periodontitis was around 44 years old and the incidence of BD increases at 50 years old in our study. Considering the onset of BD was usually in adolescence,[55] our finding was different from primary BD. However, our study showed the temporal association and long-term influence between periodontitis and BD. Therefore, we considered the BD after periodontitis may be secondary rather than primary in nature. We supposed this finding raises further concern in future study or clinical practice.

The large population-based cohort of patients constituted a strength of our study; however, several limitations should be considered when interpreting our results. First, the diagnosis of periodontitis and BD in the NHIRD was based on ICD-9-CM codes. Thus, the role of periodontitis severity in the risk of BD was not explored. Also, we could not confirm whether those patients with periodontitis having some hypomanic symptoms but not reaching or receiving the diagnosis of BD. Second, the causal relationship was assessed mainly according to the chronological order in which these 2 conditions were diagnosed; the possibility that periodontitis causes BD cannot be excluded. Third, the possibility of bias should be carefully considered because we could not exclude the possibility that BD was diagnosed soon after periodontitis, or BD was undiagnosed while the patient suffered from periodontitis. BD was reported to be genetically heterogeneous.[56] Besides, dental anxiety or fear was prevalent among patients undertaking dental procedure.[57,58] Also, dental anxiety was a highly anxious condition.[58,59] Other than anxiety, evidence had shown that affective disturbance including mood and irritability was noted as early manifestation of medical illness.[60] Therefore, those conditions may make clinical practitioners confused about whether those symptoms were reaching the diagnosis of BD. Fourth, we attempted to distinguish different subgroups, such as patients with depression, from within the bipolar cohort prior to BD diagnosis. However, BD is commonly diagnosed using only ICD-9-CM 296 in the Registry for Catastrophic Illness Patients database; therefore, clearly distinguishing these subgroups is difficult. Fifth, even though our study demonstrated the association between periodontitis and BD, whether having other factors independently cause periodontitis and BD was not investigated in our study. Finally, numerous demographic variables that might have provided useful information regarding factors possibly associated with BD and periodontitis, such as socioeconomic status, lifestyle, and family history, were unavailable. Although the prevalence of stroke in the periodontitis group was lower than the non-periodontitis group, the prevalence of HT and IHD in the periodontitis group was still higher. This might be due to the shorter follow-up period in the periodontitis group. Both HT and IHD usually occur before the onset of stroke. Because the periodontitis patients had higher risk of comorbidities, the non-periodontitis group was more active. This resulted in higher risk of head injury caused by vehicle accidents. Moreover, the patients with periodontitis might be more likely to stop drinking alcohol which may have contributed to the slightly higher (but not statistically significant) prevalence of alcohol abuse in the non-periodontitis group.

5. Conclusion

We propose that patients with periodontitis exhibit a significantly increased risk of developing BD. Accordingly, we suggest that, following the diagnosis of periodontitis, practitioners could notice the occurrence of the symptoms of BD, and associated prevention. Additional prospective studies investigating the relationship between periodontitis and BD are warranted.

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